REMARKS

In view of the following remarks, reconsideration of this application is respectfully requested.

Status of the Claims

Claims 32-41, 43, 46, and 49-52 are currently pending. Claims 1-31, 42, 44, 45, 47, 48, and 53 were previously canceled without prejudice.

Request for Continued Examination

Applicant is submitting herewith a Request for Continued Examination (RCE), which submission is in full compliance with 37 C.F.R. § 1.114. The requisite RCE fee is also being submitted herewith.

Rejections Under 35 U.S.C. § 103(a)

For an obviousness rejection to be proper, the Examiner must meet the burden of establishing that all elements of the invention are disclosed in the prior art; and must show that the prior art relied upon, or knowledge generally available in the art at the time of the invention, provides some suggestion or incentive that would have motivated the skilled artisan to modify a reference or combine references. *In re Fine*, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

"A patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). To find obviousness, the Examiner must "identify a reason that would have prompted a person of ordinary skill in the art in the relevant field to combine the elements in the way the claimed new invention does." *Id.* Therefore, in issuing an obviousness rejection, the Examiner must not simply engage in a hindsight analysis based on the disclosure of the application at issue.

In view of the following remarks and accompanying documents, the Examiner has failed to meet a *prima facie* case of obviousness. Thus, applicant respectfully submits that the rejections based on obviousness are improper and should be withdrawn.

U.S. Patent No. 6,218,420 to Dioguardi

Claims 32-41, 43, 46, and 49-52 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 6,218,420 to Dioguardi ("Dioguardi '420"). In view of the following remarks and the accompanying Declaration of Enzo Nisoli Under 37 C.F.R. § 1.132, applicant respectfully traverses this rejection.

Dioguardi '420 describes compositions based on amino acids for use in preventing and treating alimentary overloads in conditions of elevated body nitrogen requirements, without causing calcium losses. Nowhere does Dioguardi '420 teach or even suggest the composition used in the present invention (i) "for maintaining intact, restoring, and/or increasing the number of cellular mitochondria in an elderly subject" (*see* claims 32-41); or (ii) "for the treatment of apoptosis of mitochondrial origin in a subject (*see* claims 43, 46, and 49-52).

In fact, the Examiner concedes that Dioguardi '420 "does not teach the precise relative amounts of amino acids as recited in the instant claims" (Final Office Action, at page 4, last paragraph). Thus, the Examiner asserts that arriving at the composition used in the instantly claimed methods was a matter of optimization of the Dioguardi '420 composition. In particular, the Examiner alleged that, despite applicant's previous arguments against this rejection, objective evidence of nonobviousness in the form of an affidavit or declaration was needed to overcome this rejection.

In response to the Examiner's assertions, applicant submits herewith the Declaration of Enzo Nisoli Under 37 C.F.R. § 1.132 (referred to herein as the "Nisoli Decl." or the "Nisoli Delcaration"). Applicant respectfully requests that the Examiner carefully review the Nisoli Declaration, which is partially described herein below.

The Nisoli Declaration sets forth scientific reasoning, scientific evidence, and experimental results to contradict and rebut the currently pending obviousness rejection based on Dioguardi '420 (35 U.S.C. § 103(a)), as well as the nonstatutory obviousness-type double patenting rejection based on Dioguardi '420 (discussed *infra.*) (Nisoli Decl. at ¶7).

The Nisoli Declaration supports the view that it would not have been obvious or routine in view of Dioguardi '420 to arrive at the molar ratios currently recited in independent

claims 32 and 43 (Nisoli Decl. at ¶8). Further, the Nisoli Declaration states that determining the molar ratios recited in claims 32 and 43 of the subject patent application was not simply a result of optimization of the amounts and ratios of amino acids in the composition described in Dioguardi '420 (Nisoli Decl. at ¶8). Instead, making such molar ratio determinations yielded unexpected results that required extensive experimentation (Nisoli Decl. at ¶8). The Nisoli Declaration further states that the molar ratios recited in the claims are critical to the methods of independent claims 32 and 43 (Nisoli Decl. at ¶8).

As a reminder, claim 32 of the subject application recites a method for maintaining intact, restoring, and/or increasing the number of cellular mitochondria in an elderly subject. Claim 43 of the subject application recites a method of treatment of apoptosis of mitochondrial origin.

With regard to claims 32 and 43, the Examiner makes the following statement:

> The limitation in claim 32 regarding maintaining intact, restoring and/or increasing the number of cellular mitochondria and the limitation in claim 43 regarding the treatment of apoptosis of mitochondrial origin, would necessarily be present in the method taught by Dioguardi because the composition, manner of administrating it and patient population are present in the prior art.

(Final Office Action, at page 5, the second full paragraph).

As set forth in more detail below, and as set forth in the Nisoli Declaration, scientific reasoning or evidence does not support these conclusions by the Examiner (Nisoli Decl. at ¶10).

As stated in the Nisoli Declaration, a key to understanding the distinctions between the teachings of Dioguardi '420 and the claims of the subject patent application is to understand the cycle of nitrogen in the human body (Nisoli Decl. at ¶11). Nitrogen is a specific component of proteins (which are the structural elements of human body), and should be introduced daily in correct quantities to maintain the integrity of the human body and to match the daily nitrogen losses (Nisoli Decl. at ¶11). Nitrogen daily losses can be attributed to different causes, including, for example: (i) transformation of proteins to carbohydrates and lipids because of specific body needs; (ii) utilization of part of protein intake for energy purposes, for example, for balancing inadequate glucose availability, and/or (iii) intake of incorrect

proportions of amino acids (contained in food) to specific human needs with consequent occurring of high nitrogen disposal loads (Nisoli Decl. at ¶11). Thus, integrity of the human body depends on an adequate nitrogen intake (Nisoli Decl. at ¶11).

Dioguardi '420 refers to compositions based on amino acids for preventing and treating alimentary overloads in conditions of elevated body nitrogen requirements (Nisoli Decl. at ¶12). In particular, Dioguardi '420 describes diet compositions comprising specific amino acids in specific relative ratios that (a) enhance maintenance of the equilibrium between synthesis and degradation of proteins, (b) reduce the risks of under nutrition for some amino acids, and/or (c) reduce the risk of overload of those amino acids less useful to nitrogen metabolism, still maintaining easily under control the caloric input and at the same time reducing the load on disposal system of the body by minimizing catabolic products (i.e., urea, uric acid, etc.), without altering calcium excretion (Nisoli Decl. at ¶12).

By way of contrast, the present invention concerns a ***completely different*** field of medicine, even though some similarities with the composition disclosed by Dioguardi '420 can be observed (Nisoli Decl. at ¶13). The present invention deals with the problem of ***insufficient mitochondrial function*** (Nisoli Decl. at ¶13). Mitochondria are membrane-enclosed organelles found in most eukaryotic cells (Nisoli Decl. at ¶13). Mitochondria generate most of the cell's supply of adenosine triphosphate (ATP), used as a source of chemical energy (Nisoli Decl. at ¶13). In addition to supplying cellular energy, mitochondria are involved in a range of other processes, such as signaling, cellular differentiation, and cell death, as well as the control of the cell cycle and cell growth (Nisoli Decl. at ¶13). Mitochondria are implicated in several human diseases, including mitochondrial disorders and cardiac dysfunction, and play a role in the aging process (Nisoli Decl. at ¶13).

The most prominent roles of mitochondria are to produce ATP (i.e., via phosphorylation of ADP) through respiration, and to regulate cellular metabolism (Nisoli Decl. at ¶14). The central set of reactions involved in ATP production are collectively known as the citric acid cycle (Nisoli Decl. at ¶14). The production of ATP is done by oxidizing the major products of glucose, pyruvate, and NADH (Nisoli Decl. at ¶14). This process of oxidation is dependent on the presence of oxygen, and is also known as cellular aerobic respiration (Nisoli Decl. at ¶14). In the citric acid cycle done by mitochondria, each pyruvate molecule (produced

by glycolysis) is actively transported across the inner mitochondrial membrane, and into the matrix where it is oxidized and combined with coenzyme A to form CO_2, acetyl-CoA, and NADH (Nisoli Decl. at ¶14). The acetyl-CoA is the primary substrate to enter the citric acid cycle (Nisoli Decl. at ¶14). The citric acid cycle oxidizes the acetyl-CoA to carbon dioxide, and, in the process, produces reduced cofactors (NADH and $FADH_2$) that are a source of electrons for the electron transport chain, and a molecule of guanosine triphosphate, which is readily converted to an ATP (Nisoli Decl. at ¶14). During the citric acid cycle a small percentage of electrons may prematurely reduce oxygen, forming reactive oxygen species (ROS), which can cause oxidative stress in the mitochondria and may contribute to the decline in mitochondrial function associated with the aging process (Nisoli Decl. at ¶14).

As provided in the Nisoli Declaration, in view of the above, in one aspect, the present invention is based on the discovery by applicant that the administration to a mammal of specific amino acid compositions characterized by specific relative ratios of amino acids may play an important role in survival of cells and the very duration of the life of cells, since the administration of these compositions plays a role in the mitochondria life cycle and is primarily able to increase the number of mitochondria, and/or restore normal mitochondrial function (Nisoli Decl. at ¶15).

As set forth in the Nisoli Declaration, in order to illustrate the effectiveness of the invention claimed in the subject patent application, and to provide further evidence of the distinction of the claimed invention over Dioguardi '420, various experiments were designed and performed (Nisoli Decl. at ¶16). These experiments and their results are described in the Nisoli Declaration at pages 5-11, and were all performed under the direction of Dr. Nisoli (*see* Nisoli Decl. at ¶16).

Mitochondrial dysfunction due to oxidative damage is a major contributor to aging and age-related disorders, including loss of muscle mass and cardiovascular diseases (Nisoli Decl. at ¶17). The Nisoli Declaration demonstrates that a specific branched-chain amino acid mixture induces mitochondrial biogenesis in cardiac myocytes (Nisoli Decl. at ¶17).

Figures 1, 2, and 3 presented in the Nisoli Declaration summarize experimental results relating to the invention claimed in the subject patent application (Nisoli Decl. at ¶18).

Figure 1 shows that treatment of HL-l adult cardiomyocytes with the amino acid mixture of the present invention increases the mRNAs encoding mitochondrial biogenesis proteins, including peroxisome proliferator-activated receptor γ coactivator lα (PGC-lα), nuclear respiratory factor-1 (NRF-l), mitochondrial DNA transcription factor A (Tfam), and β-subunit of the mitochondrial H^+-ATP synthase (β-F1-ATPase) (Nisoli Decl. at ¶19). Mitochondrial gene targets of PGC-lα involved in oxidative phosphorylation, such as cytochrome c oxidase subunit IV (COX IV) and cytochrome c (Cyt c), were also upregulated by the amino acid mixture of U.S. Application No. 10/575,062 (Fig. 1B) (Nisoli Decl. at ¶19). These effects on gene expression translated into a 2.6-fold increase in mtDNA content (Fig. lC), a 2-fold increase in citrate synthase activity (Fig. 1D), and a 1.5-fold increase in ATP amount (Fig. 1E) by amino acids (Nisoli Decl. at ¶19).

The Nisoli Declaration states that these results strongly suggest that the amino acid mixture of the present invention is able to increase energy production in cardiomyocytes (Nisoli Decl. at ¶20). Remarkably, these results were not observed in C2Cl2 myotubes, nor L6 myoblasts treated with amino acids (Figure 2) (Nisoli Decl. at ¶20). Unlike the latter's, HL-l cells spontaneously contract *in vitro*, suggesting that the amino acid effect on mitochondrial biogenesis in muscle cells is linked to contractile activity (Nisoli Decl. at ¶20). Moreover, either white and brown adipocytes or 3T3-LI fat cells were insensitive to amino acids (Figure 3) (Nisoli Decl. at ¶20).

As stated in the Nisoli Declaration, taken together, the results presented in the Nisoli Declaration demonstrate that oral administration of the amino acid mixture of the present invention increases mitochondrial biogenesis in cardiac cells (Nisoli Decl. at ¶21). As stated by Dr. Nisoli in the Nisoli Declaration, this is an unexpected result over Dioguardi '420 (Nisoli Decl. at ¶21).

The Nisoli Declaration further states that, from the experimental tests and results, it is evident that the amino acid based compositions employed in the presently claimed method for maintaining intact, restoring, and/or increasing the number of cellular mitochondria in elderly subject and for the treatment of apoptosis of mitochondrial origin is effective in that it provides an increase in mitochondrial biogenesis and would not have been expected by one of skill in the art in view of Dioguardi (Nisoli Decl. at ¶4, page 11).

In view of the foregoing, applicant respectfully submits that the rejection of the claims for obviousness over Dioguardi '420 is improper and should be withdrawn.

U.S. Patent Application Publication No. US-2004/0157903 to Conti et al.

Claims 43, 46, and 49-52 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent Application Publication No. US-2004/0157903 to Conti et al. ("Conti '903"). In view of the following remarks, applicant respectfully traverses this rejection.

The present application and Conti '903 have a common inventor. Further, as acknowledged by the Examiner, Conti '903 would qualify as prior art **only** under 35 U.S.C. § 102(e), although applicant in no way concedes that Conti '903 is effective prior art against the present application.

Thus, as noted by the Examiner (Final Office Action, at page 10, first paragraph), this rejection can be overcome by submitting (i) an oath or declaration under 37 C.F.R. § 1.130, stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. § 104; and (ii) a terminal disclaimer in accordance with 37 C.F.R. § 1.321(c).

In response, submitted herewith is a Declaration Under 37 C.F.R. § 1.130 to Disqualify a Commonly Owned Published Patent Application as Prior Art. Also submitted herewith is a Terminal Disclaimer in accordance with 37 C.F.R. § 1.321(c).

In view of the foregoing, applicant respectfully submits that the rejection of the claims for obviousness over Conti '903 is improper and should be withdrawn.

Rejections for Nonstatutory Obviousness-Type Double Patenting

Dioguardi '420

Claims 43, 46, and 49-52 are rejected for nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 6 and 8 of Dioguardi '420. In view of the following remarks, applicant respectfully traverses this rejection.

Claim 6 of Dioguardi '420 is directed to a composition based on amino acids for treating conditions of elevated body nitrogen requirements. Claim 8 of Dioguardi '420 is

directed to a method of regulating nitrogen in a body, where the method involves administering a composition having various amino acids.

The rejected claims of the present invention are not rendered obvious by the aforementioned Dioguardi '420 claims. To support this view, applicant submits herewith the Nisoli Declaration, which is described in detail above in rebuttal of the obviousness rejection based on Dioguardi '420. Applicant requests that the Examiner consider those above arguments and the Nisoli Declaration as rebuttal of the current double patenting rejection.

In view of the foregoing, applicant respectfully submits that this rejection based on Dioguardi '420 is improper and should be withdrawn.

U.S. Patent Application Serial No. 12/104,722 to Conti

Claims 43, 46, and 49-52 are *provisionally* rejected for nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 16-35 of co-pending U.S. Patent Application Serial No. 12/104,722 to Conti et al. ("Conti '722").

This rejection is traversed in view of the Terminal Disclaimer submitted herewith in accordance with 37 C.F.R. § 1.321(c).

In view of the foregoing, applicant respectfully submits that this rejection based on the Conti '722 is improper and should be withdrawn.

CONCLUSION

Claims 32-41, 43, 46, and 49-52 are now under consideration in this case. In view of the all of the foregoing, applicant respectfully submits that the claims of the present application are in condition for allowance and such allowance is earnestly solicited.

If any unresolved issues remain that might prevent the prompt allowance of the present application, the Examiner is respectfully encouraged to contact the undersigned at the telephone number listed below to discuss these issues.

Submitted herewith via EFS-Web is payment in the amount of $490 for a two-month extension of time under 37 C.F.R. § 1.17(a)(2) (Large Entity).

Also submitted herewith via EFS-Web is payment in the amount of $810 for the RCE fee under 37 C.F.R. § 1.17(e) (Large Entity).

The Commissioner is hereby authorized to charge any fees that may have been overlooked, or to credit any overpayments of fees, to Deposit Account No. 08-1935.

Respectfully submitted,

HESLIN ROTHENBERG FARLEY & MESITI P.C.

By: **/Andrew K. Gonsalves/**

Dated: **March 29, 2010**

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